

## **REMARKS**

Reconsideration of the application is requested in view of the amendments to the claims and the remarks presented herein.

The claims in the application are claims 1, 3, 4 and 6 to 10, all other claims being cancelled.

All the claims have been rejected under 35 U.S.C. 102 as being anticipated by Halstrom and Saari patents or under 35 U.S.C. 103 as being obvious thereover and as being obvious thereover taken in view of Lihme patent. If the primary references do not anticipate the claims, Applicants have only optimized the steps of the Halstrom and Saari patents. At best, the claims differ in the use of an expanded bed which is taught by Lihme.

Applicants respectfully traverse these grounds of rejections since the cited art does not anticipate or render obvious Applicants' process of purification of N-carboxy anhydrides of amino acids (NCA) which are suspended or dissolved in an aromatic hydrocarbon, contacted with 0.5 to 10% by weight of silica to absorb impurities and then filtered to remove the silica from the solution or suspension.

In contrast thereto, Halstrom teaches purifying NCA functions by passing it through a silica gel column using chloroform as an eluant. The Saari patent teaches NCA purification by chromatography over silica gel with dry ethyl acetate as eluant.

Applicants use an aromatic hydrocarbon as a solvent which is non-polar while chloroform and dry ethyl acetate are polar solvents and Applicants do not use chromatography. As previously noted, Applicants' process comprises stirring the NCA dissolved or suspended in an aromatic hydrocarbon with 0.5 to 10% by weight of silica based on the NCA to absorb impurities thereon and then filtering to remove the silica. All these steps are now recited in the claims and clearly do not read on chromatography as alleged by the Examiner. This makes the process more economical as it uses lower amounts of silica.

As noted previously, chloroform and dry ethyl acetate are polar solvents as taught by U.S. Patent No. 4,483,979 (line 45 of column 1) and U.S. Patent No. 6,083,506 (Claim 5). U.S. Patent No. 5,925,356 teach the two solvents to be moderate polar solvents. Applicants are submitting a text by Christian Reichardt which teaches ethyl acetate is a dipolar aprotic solvent and chloroform is a miscellaneous solvent. Also enclosed is a text of Sekine et al that teaches chloroform is a moderate polar solvent and ethyl acetate is a polar solvent.


Moreover, Hansen solubility parameters Handbook submitted can be classified by their  $\delta P$  polarity component and U.S. Patent No. 6,830,630 teaches that polar solvents have a  $\delta P > 4$  and non-polar solvents have a  $\delta P < 3$ . As can be seen from the Hansen handbook, ethyl acetate has a  $\delta P = 5.3$  and is a polar solvent. Chloroform has a  $\delta P = 3.1$  and is a moderate polar solvent.

In summary, the prior art teaches chromatography of NCA which Applicants do not use and teach different solvents from Applicants. One skilled in the art would not be led to Applicants' novel process using less silica to remove impurities therefrom. Therefore,

withdrawal of these grounds of rejection is requested

In view of the amendments to the Claims and the above Remarks, it is believed that the claims point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

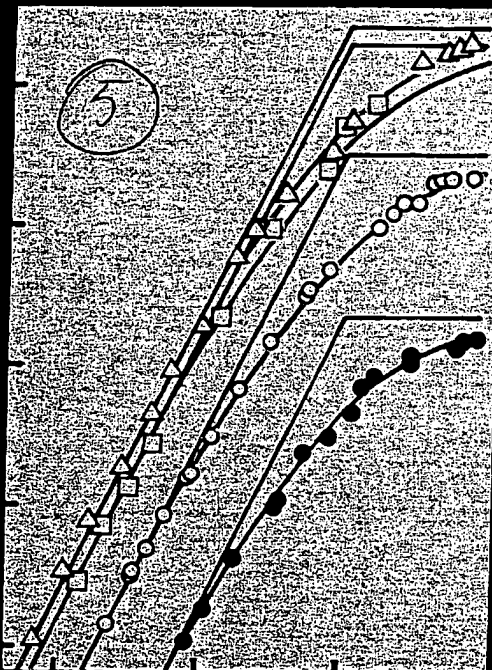
Respectfully submitted,  
Hedman and Costigan

  
\_\_\_\_\_  
Charles A. Muserlian #19,683  
Attorney for Applicants  
Tel. 212 302 8989

CAM:mlp  
Enclosures

# *Solvent Extraction Chemistry*

*Fundamentals and Applications*



*Tatsuya Sekine    Yuko Hasegawa*

## PART I. FUNDAMENTALS

he liquid category because of the organic solvents have physical and two extremes. Among these referred to in order to describe a

water is important. Sometimes the changed by a third component. later sections.

h regard to solvent extraction at thylether (bp 34.6°C) may be one igh vapor pressure at room tem- izard and possible leak of the r trouble due to a loss of materials

of a solvent is too high, special er, there may be some merit in ich as naphthalene (mp 80.05°C) l. In such systems, the solvent above the melting point of the ation is made after the two liquid ase has solidified.

solvents used for the solvent etween 0.63 g/cm<sup>3</sup> (n-pentane, 20°C). Some heavier organic obenzene, d<sub>4</sub><sup>20</sup> 1.965, and di- lom used. When the difference all, the two-phase agitation is

too-viscous solvent is not favor- nd in the phase separation. When sference of the liquid from one exanol (49.8 cp, 25°C) is an hylether (0.233 cp, 20°C) of a

Indexes of the two phases are lear. Most of the solvents used ion in the visible region but they en the UV absorption of the solute should not have overlapping her cut-off wavelength of some he most transparent solvents unfavorable for spectro-

## SOLUTIONS AND LIQUID-LIQUID SYSTEMS

45

TABLE 2.17

Cut-off Wavelength of Some Solvents

Solvent	Cut-off wavelength (nm)	Solvent	Cut-off wavelength (nm)
Water	200	Ethylacetate	270
Ethyl alcohol	210	Benzene	280
Hexane	210	Toluene	280
Cyclohexane	210	Xylene	285
Diethylether	215	Petroleum	300
Dioxane	215	Butyl alcohol	315
Acetonitrile	220	Gasoline	320
Carbon tetrachloride	220	Amyl alcohol	330
Chloroform	240	Acetone	330
Amylacetate	260	Methylethylketone	335

Source: Ref. 43, p. 103.

**Dielectric constant:** When the dielectric constant of a solvent is high, the tendency of the association of two oppositely charged particles in it is small. For some purposes, such as the extraction of ion-pairs, a solvent of high dielectric constant is desired while for other purposes, such as the diluent for organophosphoryl extractants, a solvent of low dielectric constant is desirable.

## B. Classification of Organic Solvents

## 1. Polar and Nonpolar Solvents

The terms polar solvent and nonpolar solvent are very often found in the literature. Some authors, however, prefer to describe a solvent as a "polar and high dielectric" solvent. According to them, a polar solvent consists of those molecules that have dipole moments, in other words, it consists of polar molecules.

Although the dipole moment of a liquid can be determined from the temperature dependence of the dielectric constant, these two quantities are not always conveniently interrelated, and the dielectric constant or acidity seems to be more useful for various considerations of solvent extraction than dipole moment. For example, p-xylene (dipole moment zero) does not seem to be greatly different from o-xylene (dipole moment 0.44 Debye at -20 ~ 130°) as an organic solvent in a solvent extraction system. It is also known that the solubility of an electrolyte in nitrobenzene (4.08 Debye) is usually lower than in water (1.85 Debye).

Thus the term polar solvent seems to be more often used in solvent extraction to describe a solvent that has the following properties: a large dipole moment, a high dielectric constant, and, consequently, often a large tendency for solvation.

## 2. Inert and Solvating Solvents

The term acidic solvent, or basic solvent, has also been frequently used in the literature. If the interactions between solvent molecules and solute molecules are very small, the solvent is called an inert solvent or, sometimes, an aprotic solvent. On the other hand, when the solvent molecules interact with acid or base molecules, it is called a solvating solvent or, depending on its nature, an amphiprotic solvent, acidic solvent, or basic solvent. It is also very often found that a solvent is more basic when it solvates more strongly with a metal ion.

## 3. Solvents Classified According to Their Chemical Structure and Functional Groups

### a. Hydrocarbons

Except for their use in the extraction of some simple molecules and a small number of nonpolar complexes, hydrocarbons are usually used as the diluent. As will be described, hydrocarbons, especially saturated hydrocarbons, interact with various solutes only slightly. Normal hexane and cyclohexane are the most widely used as pure solvents among nonaromatic hydrocarbons. Mixtures of nonaromatic hydrocarbons which are called petroleum ether, ligroin, and kerosene are also used very often as the organic phase, especially in large-scale operation. The interactions of nonaromatic saturated hydrocarbons with the solutes in it are the weakest compared with those in various other solvents.

Among the aromatic hydrocarbons, benzene, toluene, and xylene are very often used for solvent extraction. The interactions of these solvents with the solute are stronger than those of nonaromatic hydrocarbons, especially when  $\pi$  complexes are formed (see page 57).

### b. Halogenated Hydrocarbons

Carbon tetrachloride and chloroform are the most frequently used among halogenated hydrocarbons. Carbon tetrachloride as a solvent is similar in nature to saturated hydrocarbons, but it usually interacts with the solute somewhat more strongly. Chloroform is a useful solvent because it can work as a hydrogen-bonding acid and interact with most solute molecules more strongly than the above mentioned nonpolar solvents, but these properties are still smaller than most of the polar solvents. This "moderate" nature is favorable for many purposes.

Other halogenated hydrocarbons such as 1,2-dichloroethylene, monohalogenated benzene, and bromoform are also used in some systems.

## PART I. FUNDAMENTALS

is more often used in solvent following properties: a large and, consequently, often a large

has also been frequently used in solvent molecules and solute. It is an inert solvent or, sometimes, when the solvent molecules are called a solvating solvent or, a neutral, acidic solvent, or basic solvent is more basic when it

## Chemical Structure and Functional

some simple molecules and a carbons are usually used as the solvent, especially saturated hydrocarbons slightly. Normal hexane and other solvents among nonaromatic hydrocarbons which are called also used very often as the solvent. The interactions of non-polar solutes in it are the weakest.

benzene, toluene, and xylene are very common solvents with the aromatic hydrocarbons, especially when

is the most frequently used among solvents as a solvent is similar in that it interacts with the solute. It is a useful solvent because it can work with most solute molecules more than other solvents, but these properties are moderate. This "moderate" nature is

1,2-dichloroethylene, monochloroethylene, and so used in some systems.

## SOLUTIONS AND LIQUID-LIQUID SYSTEMS

47

## c. Alcohols

The hydroxyl group in alcohols behaves somewhat similarly to that in water; and the lower alcohols, methyl, ethyl, propyl, and tert-butyl alcohol, dissolve in any amount of water at room temperature. The solubility in water is larger in the following order: primary < secondary < tertiary alcohols. Alcohols form strong hydrogen bonds with various hydrogen bond donors and acceptors and could be good solvents for these solutes. However, for solvent extraction of metals, the oxygen in alcohols is less basic than that in ketones or ethers as long as it is in the neutral form (no dissociation of proton); and since the solvent-solvent interaction is strong, alcohols are rather similar to water. Alcohols are favorable for the extraction of ion-pairs. Those often used are n-butyl, n-amyl, isoamyl, and n-hexyl alcohols, 4-methyl-2-pentylalcohol, and cyclohexylalcohol.

## d. Ethers

In the early stage of solvent extraction chemistry, ethers were the only solvents for the extraction of metal halides and nitrates. Among the ethers, diethylether, diisopropylether, and bis(2-chloroethyl)ether have been used most frequently. Diethylether, the classic extractant, has relatively higher mutual solubility with water especially when a mineral acid is present. Diisopropylether has been used because of its smaller mutual solubility, and bis(2-chloroethyl)ether has been used because of its larger solubility for polar and ionic materials. However, although a larger accumulation of distribution data is available with ethers, most recent work indicates a preference for other solvents.

## e. Ketones

Among the various ketones, methylisobutylketone has been used most frequently. Its use is more suitable than ether due to the higher ability of coordination (more basic character of the keto oxygen than ether oxygen), higher chemical stability, and a smaller mutual solubility of it and water. This solvent is used without dilution for the extraction of various metal nitrates, halides, and other metal salts. It is also used as a diluent for some metal chelate extractants because it usually dissolves various polar solutes better than nonpolar solvents do, and it sometimes forms adduct metal chelates and enhances the extraction considerably (synergism; see Chap. 4).

## f. Esters

Various esters have been used for the extraction of metal complexes. Esters of fatty acids and aliphatic alcohols are sometimes more suitable than some other polar solvents — especially ethers — for the extraction of, for

TABLE 2.18  
Some Physical Properties of Various Organic Solvents

Solvent	Chemical formula	Molecular weight	Density (g/ml)	Viscosity (cp)	Dielectric constant	Mutual solubility		Solubility parameter $\delta$	Dipole moment
						In water (wt %)	of water (wt %)		
n-Hexane	$C_6H_{14}$	86.17	0.65937 (20°C)	0.3126 (20°C)	1.890 (20°C)	0.00095 (25°C)	0.0111 (20°C)	7.3	0.085 (20°C) (cycloheptane)
Kerosene	—	—	ca. 0.80	0.02 (20°C)	2.0-2.2	0.007 (25°C)	—	—	—
Cyclohexane	$C_6H_{12}$	84.16	0.77855	0.980	2.023 (20°C)	0.010 (20°C)	0.0055 (25°C)	8.2	—
Benzene	$C_6H_6$	78.11	0.87903 (20°C)	0.6487 (20°C)	2.283 (20°C)	0.1780 (20°C)	0.063 (25°C)	9.2	0 (20-60°C) (cyclopentane)
Toluene	$C_7H_8$	92.13	0.86694	0.5866 (20°C)	2.24 (20°C)	0.0515 (25°C)	0.0334 (25°C)	8.9	0.31 (20-60°C) (cyclopentane)
o-Xylene	$C_8H_{10}$	106.16	0.87596 (25°C)	0.756 (20°C)	2.568 (20°C)	0.0175 (25°C)	—	9.0	—
m-Xylene	$C_8H_{10}$	—	0.85990 (25°C)	0.581 (25°C)	2.374 (20°C)	0.0196 (25°C)	0.0402 (20°C)	8.8	—
p-Xylene	$C_8H_{10}$	—	0.85669 (25°C)	0.605 (25°C)	2.2599 (20°C)	0.019 (25°C)	—	8.8	—
Chloroform	$CHCl_3$	119.38	1.489 (20°C)	0.563 (20°C)	4.9 (20°C)	0.710 (17.4°C)	0.061 (17.4°C)	9.3	1.15 (25°C) (benzene)
Carbon tetrachloride	$CCl_4$	153.82	1.59472 (20°C)	0.965 (20°C)	2.205 (20°C)	0.081 (30°C)	0.011 (30°C)	8.6	0 (cyclopentane)
Chlorobenzene	$C_6H_5Cl$	112.56	1.106	0.803 (20.1°C)	5.6493 (20°C)	0.048 (30°C)	—	9.5	1.54 (25°C) (benzene)



ALIPHATIC	$\chi_T$ 118	$\chi_D$ 113	$\chi_D$ 110	$\chi_D$ 107	$\chi_D$ 104	$\chi_D$ 101	$\chi_D$ 98	$\chi_D$ 95	$\chi_D$ 92
o-Xylene	$C_8H_{10}$	106.16	0.87596 (25°C)	0.756 (25°C)	2.568 (20°C)	0.0175 (25°C)	0.0402 (20°C)	8.8	0.31 (20-50°C) (cyclopentane)
m-Xylene	$C_8H_{10}$		0.85990 (25°C)	0.581 (25°C)	2.374 (20°C)	0.0196 (25°C)	0.0402 (20°C)	8.8	—
p-Xylene	$C_8H_{10}$		0.85669 (25°C)	0.506 (25°C)	2.2599 (20°C)	0.019 (25°C)	—	8.8	—
Chloroform	$CHCl_3$	119.38	1.489 (20°C)	0.563 (20°C)	4.9 (20°C)	0.710 (17.4°C)	0.061 (17.4°C)	9.3	1.15 (25°C) (benzene)
Carbon tetrachloride	$CCl_4$	153.82	1.59472 (20°C)	0.965 (20°C)	2.205 (20°C)	0.081 (30°C)	0.011 (30°C)	8.6	0 (cyclopentane)
Chlorobenzene	$C_6H_5Cl$	112.56	1.106	0.803 (20.1°C)	5.6493 (20°C)	0.048 (30°C)	—	9.5	1.54 (25°C) (benzene)
Bromobenzene	$C_6H_5Br$	157.01	1.4951 (20°C)	1.08 (25°C)	5.53 (20°C)	0.0446 (30°C)	0.0424 (25°C)	—	1.55 (25°C) (benzene)
o-Dichloro- benzene	$C_6H_4Cl_2$	147.00	1.3064 (20°C)	—	6.8281 (25°C)	<0.026 (25°C)	0.309 (25°C)	9.9	2.27 (24°C) (benzene)
Ethylalcohol	$C_2H_5O$	46.07	0.7937 (15.6/ 15.6°C)	1.22 (20°C)	25.7 (20°C)	∞	∞	12.7	1.66 (20°C) (cyclopentane)
n-Butyl alcohol	$C_4H_{10}O$	74.12	0.9109 (20°C)	2.948 (20°C)	17.1 (25°C)	7.8 (20°C)	20.5 (25°C)	11.4	1.75 (25°C)
n-Amyl alcohol	$C_5H_{12}O$	88.13	0.82 (20°C)	3.31 (25°C)	15.8 (20°C)	1.7 (20°C)	7.46 (25°C)	10.9	1.75 (25°C)
Methylisobutyl carbinol	$C_5H_{14}O$	102.17	0.8079- 0.8080 (20°C)	—	—	1.64 (25°C)	6.35 (25°C)	10.0	—
Cyclohexanol	$C_6H_{12}O$	100.16	0.9493 (20°C)	49.8 (20°C)	15.0 (25°C)	4.00 (20.0°C)	88.93 (20°C)	11.4	—
Diethylether	$C_4H_{10}O$	74.12	0.7134 (20°C)	0.233 (20°C)	4.197 (26.9°C)	0.986 (20°C)	18.8 (20°C)	7.4	1.15 (20°C)
Isopropylether	$C_5H_{14}O$	102.17	0.72813 (20°C)	0.329 (20°C)	3.88 (25°C)	1.2 (25°C)	0.62 (20°C)	7.0	1.22 (20°C)
Dichloro- ethylether	$C_4H_8OCl_2$	143.02	1.2192 (20°C)	2.41 (20°C)	21.2 (20°C)	1.02 (20°C)	0.1 (20°C)	9.8	2.58
Acetone	$C_3H_6O$	58.08	0.7898	0.3371 (15°C)	21.45 (20°C)	∞	∞	10.0	2.69 (20°C) (cyclopentane)
Methylethyl ketone	$C_4H_8O$	72.10	0.80473 (20°C)	0.365 (30°C)	15.45 (20°C)	26.8 (20°C)	12.5 (20°C)	9.3	2.76 (25°C) (benzene)
Methylisobutyl ketone	$C_5H_{12}O$	100.16	0.8004- 0.8017 (20°C)	0.590 (20°C)	13.11 (20°C)	1.7-2.0 (20°C)	1.8-2.2 (20°C)	8.4	—

TABLE 2.16 (Continued)

Solvent	Chemical formula	Molecular weight	Density (g/ml)	Viscosity (cp)	Dielectric constant	Mutual solubility		Solubility parameter	Dipole moment
						in water (wt %)	of water (wt %)		
Cyclohexanone	$C_6H_{10}O$	98.14	0.95044 (15°C)	2.453 (15°C)	18.3 (20°C)	2.3 (20°C)	8.0 (20°C)	9.9	3.02 (25°C) (benzene)
Ethylacetate	$C_4H_8O_2$	88.10	0.902 (20°C)	0.45 (20°C)	6.02 (25°C)	7.9 (15°C)	ca. 3.6	9.1	1.88 (25°C) (benzene)
Butylacetate	$C_8H_{16}O_2$	116.16	0.882 (20°C)	0.693 (25°C)	5.01 (20°C)	1.0 (20°C)	1.37 (20°C)	8.5	1.84 (22°C) (benzene)
Amylacetate	$C_7H_{14}O_2$	130.18	0.879 (20°C)	0.924 (20°C)	4.75 (20°C)	0.17 (20°C)	1.15 (20°C)	8.5	1.91 (benzene)
Acetic acid	$C_2H_4O_2$	60.05	1.04923 (20°C)	1.3 (18°C)	6.170 (20°C)	∞	∞	—	1.68 (30°C) (benzene)
Butyric acid	$C_4H_8O_2$	88.10	0.9590 (20°C)	1.61 (20°C)	2.97 (25°C)	∞	∞	—	1.65 (30°C) (benzene)
Caproic acid	$C_6H_{12}O_2$	116.16	0.93136 (15°C)	2.814 (15°C)	2.63 (20°C)	0.958 (20°C)	—	—	1.13 (25°C) (benzene)
Nitromethane	$CH_3NO_2$	61.04	1.139 (20°C)	0.632 (25°C)	39 (20°C)	11.1 (25°C)	2.09 (25°C)	12.7	3.56 (20°C) (cyclopentane)
Nitroethane	$C_2H_5NO_2$	75.07	1.052 (20°C)	0.661 (25°C)	28.06 (30°C)	4.68 (25°C)	1.05 (25°C)	11.7	3.60 (20°C) (n-hexane)
Nitrobenzene	$C_6H_5NO_2$	123.11	1.19833 (25°C)	2.165 (15°C)	34.82 (25°C)	0.19 (25°C)	0.24 (20°C)	10.4	4.03 (25°C) (benzene)
Aniline	$C_6H_7N$	93.12	1.02173 (20°C)	3.176 (30°C)	7.06 (20°C)	3.7 (30°C)	5.4 (20°C)	—	1.51 (25°C) (benzene)
Carbon disulfide	$CS_2$	76.14	1.27055 (15°C)	0.363 (20°C)	2.641 (20°C)	0.169 (25°C)	0.10 (25°C)	10.0	0.06 (25°C) (benzene)
TBP	$C_{12}H_{27}O_4P$	266.32	0.9766 (28°C)	4	7.959 (30°C)	0.039 (25°C)	4.67 (25°C)	8.8	3.07 (25°C) (benzene)

		110.12	90.000	44.012	44.00	90.000	1.13 (40°C)
Nitromethane	CH <sub>3</sub> NO <sub>2</sub>	61.04	1.139	(15°C)	(15°C)	39	3.56 (20°C)
Nitroethane	C <sub>2</sub> H <sub>5</sub> NO <sub>2</sub>	75.07	1.052	(20°/4°)	(25°C)	28.06	3.60 (20°C)
Nitrobenzene	C <sub>6</sub> H <sub>5</sub> NO <sub>2</sub>	123.11	1.19833	(20°/20°)	(25°C)	34.82	4.03 (25°C)
Aniline	C <sub>6</sub> H <sub>7</sub> N	93.12	1.02173	(25°/4°)	(15°C)	7.06	1.51 (25°C)
Carbon disulfide	CS <sub>2</sub>	76.14	1.27055	(20°C)	(30°C)	2.841	0.06 (25°C)
TBP	C <sub>12</sub> H <sub>27</sub> O <sub>4</sub> P	266.32	0.9766	(15°C)	(20°C)	7.959	3.07 (25°C)
				4	(30°C)	0.039	8.8
					(28°C)	(25°C)	(benzene)

## SOLUTIONS AND LIQUID-LIQUID SYSTEMS

51

example, metal halides. However, most esters tend to hydrolyze to the acid and the alcohol, especially in acid solution, and hence the use of esters of fatty acid-aliphatic alcohols has become less frequent. Esters of phosphoric acid and aliphatic alcohols, such as tributylphosphate, are also very important. They are used without dilution or after dilution with a nonpolar solvent, as will be described in Chaps. 4 and 7.

### g. Nitrogen-Containing Solvents

Various amines have been employed very widely as solvents. However, since they are usually used after dilution, they will be described in Chaps. 4 and 7. Apart from amines, the important nitrogen-containing solvents are nitrobenzene and nitromethane. Since these solvents have very high dielectric constants and relatively low mutual solubilities with water, they are frequently used for the extraction of ion-pairs.

The physical properties of various solvents are given in Table 2.18 [4, 42, 43].

### C. Organic Solutions

## 1. Dissolution of Materials in Organic Solvents

The dissolution process of materials in organic solvents can be described in the same manner as for aqueous solutions. Since the energy necessary for the separation of solute molecules in the liquid or solid state into isolated molecules is the same in all cases, the main difference in the dissolution in organic solvents and that in water are found in the other two steps as follows.

Destruction of solvent-solvent interaction: In order to bring a separate solute molecule into an organic solvent, it is necessary to break down the solvent-solvent interaction. In comparison with water, in which the molecules interact very strongly with each other by hydrogen bonds, the intermolecular force in organic solvents is usually much smaller and the enthalpy change in this process is, in general, smaller than that in water. This change becomes larger as the polarity of the solvent molecules increases and is much larger when hydrogen bonds are formed, as in alcohols.

Formation of solute-solvent interaction: the solute-solvent interaction is quite different when the natures of the solute and the solvent are different. The interaction is the smallest when both of them are nonpolar, it becomes stronger as the polarity of the molecules increases, and it is the strongest when there are interactions due to the formation of hydrogen bonds, charge transfer complexes, or coordination complexes.

# HANSEN SOLUBILITY PARAMETERS

A USER'S HANDBOOK

Charles M. Hansen



CRC PRESS

TABLE A.1 (continued)  
Hansen Solubility Parameters for Selected Solvents (Solvents are in Alphabetical Order)

No.	Solvent	Dispersion	Polar	Hydrogen Bonding	Molar Volume
150	3-CHLOROBENZYLCHLORIDE	19.9	9.3	2.6	117.7
151	1,2-CHLOROBROMOETHYLENE	17.2	6.6	2.3	78.7
152	1-CHLOROBUTANE	16.2	5.5	2.0	104.5
750	2-CHLOROBUTANE	15.8	7.6	2.0	106.8
780	2-CHLOROCYCLOHEXANONE	18.5	13.0	5.1	113.9
153	CHLOROCYCLOPROPANE	17.6	7.2	2.2	84.9
154	CHLORODIFLUOROMETHANE (FREON 22)	12.3	6.3	5.7	72.9
155	N-CHLORODIMETHYLAMINE	16.0	7.8	7.9	87.4
772	2-CHLOROETHYL ACETATE	16.7	9.6	8.8	107.5
756	2-CHLOROETHYL ETHYL ETHER	16.3	7.9	4.6	109.5
834	2-CHLOROETHYL ETHYL SULFIDE	17.2	5.0	6.1	116.9
808	o-CHLOROFLUOROBENZENE	19.4	8.7	2.0	104.9
156	CHLOROFORM	17.8	3.1	5.7	80.7
157	BIS(CHLOROMETHYL) ETHER	17.2	4.9	6.6	86.6
158	CHLOROMETHYLSULFIDE	16.6	6.4	2.0	95.0
809	p-CHLORONITROBENZENE	20.4	9.6	4.2	103.7
159	CHLORONITROMETHANE	17.4	13.5	5.5	65.1
160	2-CHLOROPHENOL	20.3	5.5	13.9	102.3
161	CHLORPRENE	16.1	5.4	2.1	93.2
162	2-CHLOROPROPENAL	17.1	12.9	8.1	75.5
163	CHLOROPROPENE	15.3	6.9	2.2	82.3
164	2-CHLOROPROPENOIC ACID	19.1	9.4	12.4	86.6
165	3-CHLOROPROPIONALDEHYDE	17.0	13.3	8.2	73.0
166	CHLOROPROPIONITRILE	17.3	15.9	6.1	77.4
167	3-CHLOROPROPYNE	16.7	7.4	2.3	72.4
711	p-CHLOROSTYRENE	18.7	4.3	3.9	128.3
712	o-CHLOROSTYRENE	18.7	4.7	3.9	126.8
168	4-CHLOROTHIOPHENOL	20.8	8.6	10.6	100.0
787	o-CHLOROTHIOPHENOL	20.2	7.0	10.0	113.4
814	p-CHLOROTOLUENE	19.1	6.2	2.6	118.3
134	CHLOROTRIFLUOROETHYLENE (CTFE)	15.3	6.3	0.0	75.6
169	m-CRESOL	18.0	5.1	12.9	104.7
170	CROTONALDEHYDE	16.2	14.9	7.4	82.5
171	CROTONIC ACID	16.8	8.7	12.0	84.6
172	CROTONLACTONE	19.0	19.8	9.6	76.4
173	TRANS-CROTONONITRILE	16.4	18.8	5.5	81.4
174	CYANAMID (CARBAMONITRILE)	15.5	17.6	16.8	32.8
175	CYANOGEN	15.1	11.8	0.0	54.6
176	CYANOGEN BROMIDE	18.3	15.2	0.0	52.6
177	CYANOGEN CHLORIDE	15.6	14.5	0.0	51.8
178	CYCLOBUTANONE	18.3	11.4	5.2	73.4
179	CYCLODECANONE	16.8	8.0	4.1	161.0
180	CYCLOHEPTANONE	17.2	10.6	4.8	118.2
181	CYCLOHEXANE	16.8	0.0	0.2	108.7
182	CYCLOHEXANOL	17.4	4.1	13.5	106.0
183	CYCLOHEXANONE	17.8	6.3	5.1	104.0
184	CYCLOHEXYLAMINE	17.2	3.1	6.5	113.8
185	CYCLOHEXYLCHLORIDE	17.3	5.5	2.0	118.6

**TABLE A.1 (continued)**  
**Hansen Solubility Parameters for Selected Solvents (Solvents are in Alphabetical Order)**

No.	Solvent	Dispersion	Polar	Hydrogen Bonding	Molar Volume
289	N,N-DIMETHYL BUTYRAMIDE	16.4	10.6	7.4	127.8
290	DIMETHYL CARBONATE	15.5	3.9	9.7	84.2
291	DIMETHYL CELLOSOLVE	15.4	6.0	6.0	104.5
292	DIMETHYL DIETHYLENE GLYCOL	15.8	6.1	9.2	142.0
293	DIMETHYL DIKETONE	15.7	5.3	11.7	88.2
294	DIMETHYL DISULFIDE	17.3	7.8	6.5	88.6
295	DIMETHYL ETHANOLAMINE	16.1	9.2	15.3	101.1
296	DIMETHYL ETHER	15.2	6.1	5.7	63.2
297	DIMETHYL FORMAMIDE	17.4	13.7	11.3	77.0
298	1,1-DIMETHYL HYDRAZINE	15.3	5.9	11.0	76.0
299	DIMETHYL KETENE	15.2	7.4	4.8	87.6
839	DIMETHYL METHYL PHOSPHONATE	16.7	13.1	7.5	106.9
849	2,6-DIMETHYL PHENOL	19.1	4.9	12.9	116.3
850	3,4-DIMETHYL PHENOL	19.2	6.0	13.4	121.0
300	DIMETHYL PHTHALATE	18.6	10.8	4.9	163.0
782	2,5-DIMETHYL PYRROLE	18.3	7.6	6.8	101.8
301	DIMETHYL SULFIDE	16.1	6.4	7.4	73.2
302	DIMETHYL SULFONE	19.0	19.4	12.3	75.0
303	DIMETHYL SULFOXIDE	18.4	16.4	10.2	71.3
304	2,3-DIMETHYL-1-BUTENE	14.9	1.2	2.8	125.2
305	DIOCTYL PHTHALATE	16.6	7.0	3.1	377.0
306	1,4-DIOXANE	19.0	1.8	7.4	85.7
307	1,3-DIOXOLANE	18.1	6.6	9.3	69.9
308	DIPROPYL AMINE	15.3	1.4	4.1	136.9
737	DIPROPYL KETONE	15.8	5.7	4.9	140.8
309	DIPROPYLENE GLYCOL	16.5	10.6	17.7	130.9
310	DIPROPYLENE GLYCOL METHYL ETHER	15.5	5.7	11.2	157.4
311	DIPROPYLENE GLYCOL MONOMETHYL ETHER ACETATE	16.3	4.9	8.0	195.7
312	2,3-DITHIABUTANE	17.3	7.8	6.5	88.6
313	DITRIDECYL PHTHALATE	16.6	5.4	1.9	558.3
314	p-DIVINYL BENZENE	18.6	1.0	7.0	142.8
315	DIVINYL SULFIDE	16.5	4.6	5.6	93.6
316	DODECANE	16.0	0.0	0.0	228.6
317	EICOSANE	16.5	0.0	0.0	359.8
318	EPICHLOROHYDRIN	18.9	7.6	6.6	78.4
319	1,2-EPOXY PROPENE	16.5	8.6	6.7	70.0
320	3,4-EPOXY-1-BUTENE	16.6	7.7	7.4	80.7
321	EPSILON-CAPROLACTAM	19.4	13.8	3.9	110.7
322	1,2-ETHANE DITHIOL	17.9	7.2	8.7	83.9
323	ETHANESULFONYLCHLORIDE	17.7	14.9	6.8	94.7
324	ETHANETHIOL (ETHYL MERCAPTAN)	15.7	6.5	7.1	74.3
325	ETHANOL	15.8	8.8	19.4	58.5
326	ETHANOLAMINE	17.0	15.5	21.2	59.8
794	4-ETHOXY ACETOPHENONE	18.8	10.3	6.4	162.6
776	1-ETHOXY ETHOXY-2-PROPANOL	15.9	5.7	11.7	156.0
761	3-ETHOXY PROPIONALDEHYDE	16.0	8.8	7.4	112.1
327	ETHOXYETHYL PROPIONATE	16.2	3.3	8.8	155.5
328	ETHYL ACETATE	15.8	5.3	7.2	98.5

PARIS XLORSAY\_BU SCIENCES



D

953 001667 4



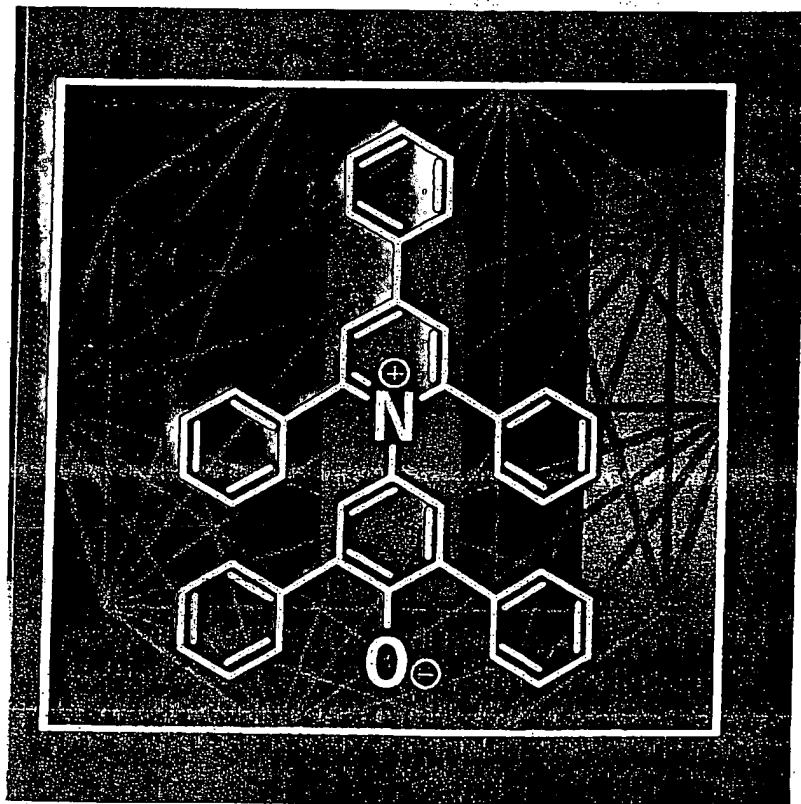
WILEY-VCH



Christian Reichardt

# Solvents and Solvent Effects in Organic Chemistry

Third, Updated and Enlarged Edition



The most ambitious approach to a general classification of solvents by PCA has been that of Chastrette *et al.* [138]. His classification is based on the representation of solvents as points in an eight-dimensional property space, using the Kirkwood function  $(\epsilon_r - 1)/(2\epsilon_r + 1)$ , molar refraction  $V_m \cdot (n^2 - 1)/(n^2 + 2)$ , Hildebrand's  $\delta$  parameter [cf. Eq. (2-1) in Section 2.1], refractive index, boiling point, dipole moment, and the HOMO and LUMO energies as solvent descriptors. Five descriptors are the properties of bulk solvents, whereas the last three ( $\mu$ , HOMO, and LUMO) are molecular properties. The calculated HOMO and LUMO energies of the solvents are included in the set of basic variables in order to take into account Lewis acid/base interactions between solute and solvent. Because some of the eight descriptors are linearly correlated to each other, the spatial dimensionality needed to describe the solvent classification should be lower than eight.

Indeed, it was possible to reduce the original eight-dimensional space by suppressing five principal components, providing an easily visualised three-dimensional solvent property space, with only an 18% loss of information. This subspace is defined by the principal components  $F_1$  (strongly correlated with the molar refraction, refractive index, and HOMO energy),  $F_2$  (strongly correlated with the Kirkwood function, dipole moment, and boiling point), and  $F_3$  (strongly correlated with the LUMO energy). Therefore,  $F_1$  can be interpreted as an index of the polarizability of the solvent,  $F_2$  represents the polarity of the solvent, and  $F_3$  can be explained by the electron affinity and Lewis acidity of the solvent. The Lewis basicity of the solvent seems to be included in  $F_1$ .

The 83 organic solvents have been grouped into *nine classes* from the clustering of their principal component values, using a nonhierarchical multivariate taxonomy to progressively classify solvents by means of the discriminating power of the eight descriptors (cf. Fig. 3-6).

Classes (1) ... (3) comprise dipolar aprotic\* solvents. The first class (AD) contains the usual protic solvents having a relative low dipolarity ( $\mu \leq ca. 12 \cdot 10^{-30}$  Cm). More dipolar aprotic solvents ( $\mu \geq ca. 12 \cdot 10^{-30}$  Cm) are found in the second class (AHD). A third class (AHDP) contains only two members, differing from the second by their high polarizability.

Classes (4) ... (6) include apolar aprotic\* solvents. In classes (4) and (5), ARA and ARP, are found aromatic apolar ( $\mu \approx 0 \dots 4 \cdot 10^{-30}$  Cm) and aromatic relatively dipolar solvents ( $\mu \approx 4 \dots 10 \cdot 10^{-30}$  Cm). Class (6), called EPD, consists of solvents that are typical electron pair donors ( $\mu \approx 4 \dots 10 \cdot 10^{-30}$  Cm).

Protic or HBD solvents are found in classes (7) and (8). These two classes of hydrogen-bonding solvents (HB and HBSA) are clearly separated by the degree of their intermolecular association. If a total of ten solvent classes are established, water would then constitute a subclass of class HBSA.

Lastly, class (9), labelled MISC (from miscellaneous), consists of four solvents, which have only their high polarizabilities in common.

\* Bordwell *et al.* [135] have pointed out that solvents referred to as *dipolar aprotic* are in fact not aprotic. In reactions employing strong bases their protic character can be recognized. Therefore, instead of *dipolar aprotic* the designation *dipolar nonhydroxylic* or better *dipolar non-HBD* solvents is strongly recommended. Cf. Section 2.2.5 and 3.4 (footnote). In order to avoid confusion, the nomenclature proposed by Chastrette *et al.* [138] is retained in Fig. 3-6.



## 3.5 Classification of Solvents using Multivariate Statistical Methods 89

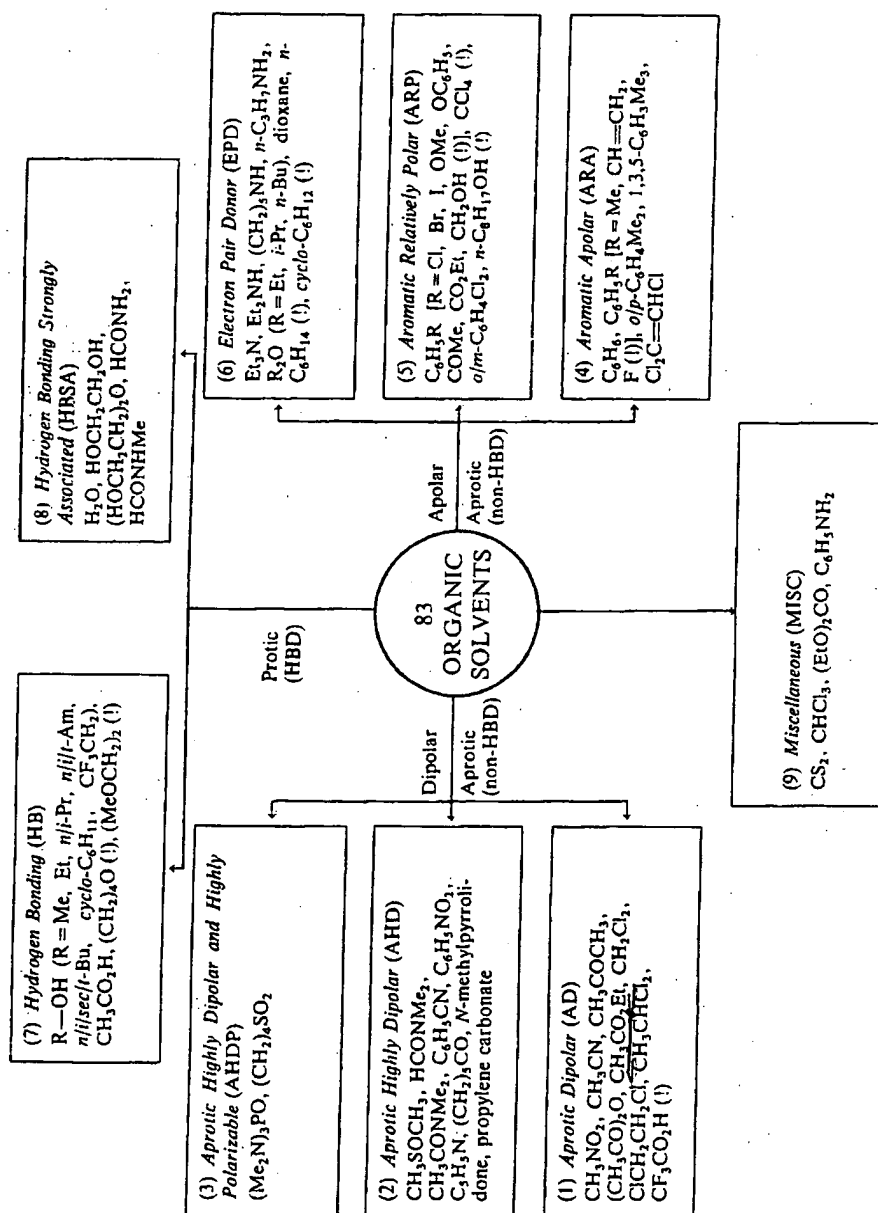


Fig. 3-6. Chastrette's classification of organic solvents [138].

## Appendix 491

Table A-9. Compilation of solvents commonly used for crystallization of organic compounds<sup>a)</sup>, listed in order of decreasing solvent polarity as measured by the  $E_T^N$  values<sup>b)</sup>.

Solvent	$E_T^N$	$t_{bp}/^{\circ}\text{C}$	Suitable solvent for	Second solvent for mixture <sup>c)</sup>
Water	1.000	100.0	Salts, amides, some carboxylic acids	Acetone, alcohols, 1,4-dioxane, acetonitrile
Methanol	0.762	64.5	General, esters, nitro and bromo compounds	Water, diethyl ether, benzene
2-Methoxyethanol	0.657	124.6	Sugars	Water, benzene, diethyl ether
Ethanol	0.654	78.3	General, esters, nitro and bromo compounds	Water, hydrocarbons, ethyl acetate
Acetic acid	0.648	117.9	Salts, amides, some carboxylic acids	Water
Acetonitrile	0.460	81.6	Dipolar compounds	Water, diethyl ether, benzene
Acetone	0.355	56.1	General, nitro and bromo compounds, osazones	Water, hydrocarbons, diethyl ether
Dichloromethane	0.309	39.6	General, low-melting compounds	Ethanol, hydrocarbons
Pyridine	0.302	115.3	High-melting, poorly soluble compounds	Water, methanol, hydrocarbons
Trichloromethane	0.259	61.2	General, acid chlorides	Ethanol, hydrocarbons
Methyl acetate	0.253	56.9	General, esters	Water, diethyl ether
Ethyl acetate	0.228	77.1	General, esters	Diethyl ether, benzene, hydrocarbons
1,4-Dioxane	0.164	101.3	Amides	Water, benzene, hydrocarbons
Diethyl ether	0.117	34.5	General, low-melting compounds	Acetone, hydrocarbons
Benzene	0.111	80.1	Aromatics, hydrocarbons, molecular complexes	Diethyl ether, ethyl acetate, hydrocarbons
Toluene	0.099	110.6	Aromatics, hydrocarbons	Diethyl ether, ethyl acetate, hydrocarbons
Tetrachloromethane	0.052	76.7	Apolar compounds, acid chlorides, anhydrides	Diethyl ether, benzene, hydrocarbons
Ligroin	—	90–110	Hydrocarbons	Ethyl acetate, benzene, dichloromethane
Petroleum ether	—	40–60	Hydrocarbons	Any solvent on this list from ethanol down
n-Hexane	0.009	68.7	Hydrocarbons	Any solvent on this list from ethanol down
Cyclohexane	0.006	80.8	Hydrocarbons	Any solvent on this list from ethanol down

<sup>a)</sup> Cf. A. J. Gordon and R. A. Ford: *The Chemist's Companion – A Handbook of Practical Data, Techniques, and References*. Wiley, New York, London, Sydney, Toronto, 1972, p. 442.

<sup>b)</sup> C. Reichardt, *Chem. Rev.* 94, 2319 (1994).

<sup>c)</sup> Trial and error is usually required in selecting a second solvent for a mixture. There are some generally successful mixtures, such as diethyl ether/methanol (or ethanol) for highly associated solids (especially amides and alcohols) and many natural products, and diethyl ether/petroleum ether (or benzene) for dipolar compounds (especially esters and alcohols) and hydrocarbons<sup>a)</sup>. Cf. also J. B. Baumann: *Solvent Selection for Recrystallization*. *J. Chem. Educ.* 56, 64 (1979); R. E. R. Craig: *Rapid, Efficient Determination of Recrystallization Solvents at the Microscale Level*, *J. Chem. Educ.* 66, 88 (1989).

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**